New Pathways to Discovery

The human body is dauntingly complex. To truly revolutionize medicine and improve human health, we need a more detailed understanding of the vast networks of molecules that make up our cells and tissues, their interactions, and their regulation. We also must have a more precise knowledge of the combination of molecular events leading to disease. New Pathways to Discovery is the NIH Roadmap theme that sets out to advance our understanding of biological systems and to build a better "toolbox" for medical research in the 21st century.

To capitalize on the completion of the human genome sequence and recent exciting discoveries in molecular and cell biology, the research community needs wide access to technologies, databases, and other scientific resources that are more sensitive, more robust, and more easily adaptable to researchers' individual needs. Resources will be developed and made available through five components of the New Pathways to Discovery theme. They are: Building Blocks, Biological Pathways, and Networks; Molecular Libraries & Molecular Imaging; Structural Biology; Bioinformatics and Computational Biology; and Nanomedicine. Grants and contracts were awarded in fiscal year (FY) 2004 within each of these areas to support strategies for diagnosing, treating, and preventing disease. Summaries of those projects are provided below.

Building Blocks, Biological Pathways, and Networks

Complex elements—from individual genes to entire organs—work together in a feat of biological teamwork to promote normal development and sustain health. These systems work because of intricate and interconnected pathways that enable communication among genes, molecules, and cells. Scientists are still working to discover all of these pathways and to determine how disturbances in them may lead to disease.

A central component of an organism's biological pathways and networks is the set of proteins encoded by its genome, commonly referred to as the proteome. This NIH Roadmap initiative promotes the development of new proteomic technologies to enable researchers to expand the identification of biological pathways with the ultimate goal being to understand diseases involving such pathways and, ideally, to develop potential treatments.

Another critical focus is providing researchers with novel analytical tools to better understand the metabolic components and networks within the cell, commonly referred to as the metabolome. Ultimately, scientists hope to be able to completely map an organism's protein and metabolism networks, and create models to help predict the human body's response to disease, injury, or infection. The two solicitations in this area are described below.

National Technology Centers for Networks and Pathways

This initiative will encourage the development of highly sensitive tools to quantitatively measure the activity, translocation, and interactions of intracellular protein molecules. The National Technology Centers for Networks and Pathways will cooperate in a networked, national effort to develop highly novel technologies in the field of proteomics. These technologies will be directed at gathering information at the level needed to characterize sub-cellular processes. Beyond the cataloguing of proteins and their interactions within cells, these methods will be aimed at defining the dynamics of complex intracellular systems. Ultimately, additional research grants supported by individual NIH Institutes will leverage the advanced technologies in the centers to address a broad range of challenging biomedical research problems. Initial centers were funded in FY2004; this RFA was also reissued for FY2005.

Metabolomics Technology Development

The emerging field of metabolomics seeks to understand all the small molecules found within cells and tissues. To date, there is no single technology that can effectively measure, with sufficient sensitivity and precision, the diverse range of metabolites and their dynamic fluctuations within cells. This initiative will encourage the development of highly innovative and sensitive tools to identify and quantify cellular metabolites. The technologies developed under this initiative will make a major contribution to research on the chemical and molecular pathways in cells involved in development, normal function, aging, and disease.

Molecular Libraries & Molecular Imaging

The Molecular Libraries initiative will provide public sector biomedical researchers access to small organic molecules that can be used as chemical probes to study the functions of genes, cells, and biochemical pathways in health and disease. The component is also expected to facilitate the development of new drugs by providing early stage chemical compounds to researchers so they can find successful matches between a chemical and its target and thus help validate new targets with potential for therapeutic intervention.

Unlike anatomical imaging, molecular imaging is an emerging research area that aims to display the biochemical and physiological abnormalities that underlie disease, rather than simply show the consequences of these abnormalities. The Molecular Imaging initiative will enhance the discovery and availability of technologies and reagents for imaging of molecules or molecular events within single cells and whole organisms. The ultimate goal is to enable a detailed molecular understanding of cell and tissue function in normal and disease states, which may lead to greater power to diagnose and treat disease.

Molecular Libraries Small Molecule Repository

The Small Molecule Repository will acquire, maintain, and distribute a collection of up to 500,000 compounds, obtained from both commercial and academic sources, with diverse chemical structures and known or unknown biological activities. The repository, funded in FY2004, will provide these compounds to the Molecular Libraries Screening Centers Network (MLSCN) for use in high-throughput screening (HTS) of a diverse set of biological assays submitted by the research community and implemented within the centers. It is anticipated that screening "hits" will be further developed into optimized chemical analogs that can be used by the scientific community as bioactive probes to study molecular targets and cellular pathways,

and potentially as starting points for therapeutics development outside of the MLSCN. The probes will be available to researchers via the repository, and the chemical structures of the compounds in the repository, along with the associated screening data obtained from the MLSCN, will be shared with the public through PubChem (http://pubchem.ncbi.nlm.nih.gov).

Molecular Libraries Screening Centers Network

The Molecular Libraries Screening Centers Network (MLSCN) will be a national resource to empower scientists to explore biology using small molecules. This initiative will provide researchers in the public and private sectors with small molecules and will be linked to a larger database of biological information on small organic molecules (PubChem). These compounds will be useful as biological probes for the study of molecular and cellular pathways and phenotypes, and their functions in health and disease. The initial network will be a three-year pilot program funded in FY2005.

Molecular Libraries Screening Instrumentation

The Molecular Libraries Screening Instrumentation (MLSI) initiative is designed to develop innovative instrumentation that can be integrated with high-throughput screening (HTS) systems to identify small molecules to explore the biological mechanisms within living cells. HTS allows automated testing of vast numbers of these molecules at an extremely rapid rate. This initiative seeks to develop HTS instrumentation that will be faster, more efficient, and more accurate than currently available systems. Such new technologies will be necessary to achieve the ambitious goals of the Molecular Libraries Initiative to discover probes for biological processes on an unprecedented scale. These investigations will ultimately lead to the identification of novel targets for the treatment of disease.

High-Throughput Molecular Screening Assay Development

High-throughput screening (HTS) has great potential to provide insights into the mechanisms of cellular biology and disease, but to date use of the technology has been limited because of inadequate access to screening facilities and compound libraries. This initiative will provide unprecedented access to these resources and allow a much broader research application of HTS. Its goal is to create a continuous stream of biological assays that can be used for automated screening at the NIH Molecular Libraries Screening Centers. The initiative will emphasize assays that provide insight into new cellular or molecular targets that have not been the focus of current HTS approaches.

Innovation in Molecular Imaging Probes

Molecular imaging is an emerging research area aimed at imaging specific molecular pathways in living tissues and cells, particularly those that are key targets in disease processes. Unlike anatomical imaging, molecular imaging displays the biochemical and physiological abnormalities that underlie disease, rather than simply the consequences of these abnormalities. Thus far, however, these methods have been limited by the poor sensitivity and specificity of currently used molecular probes. This initiative will encourage the development of new probes that will achieve an improvement of one-to-two orders of magnitude in the ability to detect and image specific molecular events *in vivo*. The new probes will also have potential for clinical applications.

Development of High-Resolution Probes for Cellular Imaging

The goal of this initiative is to create molecular probes and imaging systems that are sensitive enough to detect and image individual molecules within living cells. The information gleaned will allow significant new insights into cellular processes, events, and changes over time. The improved technology that will result from these efforts will increase the resolution of the images within living cells by 10-100-fold and will constitute an important step forward in understanding cell biology.

Structural Biology

Proteins are indispensable molecules in our bodies, and each has a unique three-dimensional shape that is well-suited for its particular job. Some proteins build our cells and others work like miniature machines to allow us to think, smell, eat, and breathe. If the shape of even one protein goes awry, there can be major consequences for human health, such as cystic fibrosis, Alzheimer's disease, and countless other diseases.

The NIH Roadmap Structural Biology initiative is an effort to create a "picture gallery" of the molecular shapes of proteins in the body and is designed to advance our understanding of how proteins and their component parts function in the body. As an initial step, this will require the development of rapid, efficient, and dependable methods to produce protein samples that scientists can use to determine the structure of proteins and clarify the role of protein shape in normal and abnormal protein function. The data and tools will be shared with researchers across the Nation. In later years, the initiative will focus on finding ways to discern structures of protein biomolecular “machines”—sets of proteins that act together to carry out essential cellular functions.

Innovation in Membrane Protein Production

Centers with the goal of developing novel approaches to preparing membrane proteins that are structurally and functionally intact were awarded in FY2004. The centers are expected to develop new methods to produce significant amounts of proteins for subsequent structural studies. They will disseminate their data through websites and publications and the research community will have access to their novel methods, materials, and facilities.

Bioinformatics and Computational Biology

The NIH Roadmap is paving a future "information superhighway" dedicated to advancing medical research. Scientists today are using computers and robots to separate molecules in solution, read genetic information, reveal the three-dimensional shapes of proteins, and take pictures of the brain in action. These techniques generate huge amounts of data, and biology is changing fast into a science of information management.

Researchers need software programs and other tools to analyze, integrate, visualize, and model these data. Through the Bioinformatics and Computational Biology initiative, researchers will be able to seamlessly share data gathered from large experiments, such as the role of heredity in individuals' different responses to medicines.

National Centers for Biomedical Computing
This initiative will create a networked computational infrastructure for the Nation's biomedical computing needs. The centers will also play a major role in educating and training researchers to engage in biomedical computing. The centers were funded in FY2004 and have been reissued for FY2005.

Nanomedicine

A long-term goal of this NIH Roadmap is to create materials and devices at the level of molecules and atoms to cure disease or repair damaged tissues, such as bone, muscle, or nerve. A nanometer is one-billionth of a meter, too small to be seen with a conventional lab microscope. And it is at this scale that biological molecules and structures inside living cells operate. Researchers have set their sights on replacing broken parts of a cell with miniature biological devices and searching out and destroying infectious agents before they do harm.

Nanomedicine Center Concept Development Awards
This initiative represents the first step in a novel process to develop a network of Nanomedicine Development Centers. The centers will focus on developing methods to precisely define the physical characteristics of structures inside cells at the molecular level. Teams of scientists from an array of disciplines, including cell biology, biochemistry, mathematics, physics and engineering, will work together to develop new technologies, enabling them to better understand the molecular interactions within living cells and the physical and chemical properties of molecular structures at the nanoscale. This knowledge will also lead to a deeper understanding of biological design principles, which may one day permit scientists to engineer or repair molecular structures in order to treat diseased or damaged cells and tissues. Awards made in FY2004 will support planning activities for the development centers that will be funded in FY2005 and FY2006.

The NIH Roadmap for Medical Research is a series of far-reaching initiatives designed to transform the Nation's medical research capabilities and speed the movement of scientific discoveries from the bench to the bedside. It provides a framework of the priorities the NIH must address in order to optimize its entire research portfolio and lays out a vision for a more efficient and productive system of medical research. Additional information about the NIH Roadmap can be found at http://nihroadmap.nih.gov. For more information on the New Pathways to Discovery initiatives, please go to http://nihroadmap.nih.gov/newpathways/index.asp.

The National Institutes of Health (NIH), an agency of the U.S. Department of Health and Human Services, is the primary Federal agency for conducting and supporting basic, clinical, and translational medical research. NIH is comprised of 27 institutes and centers and investigates the causes, treatments, and cures for both common and rare diseases. For more information on the NIH, please visit the NIH Web site at http://www.nih.gov.